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IN THE INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY (IPEA/US)

In re:	International Patent Application of Douglas E. Kligman *et al.*	: Authorized Officer: **J. Venkat**
International Appln. No.:	PCT/US97/01919	:
International Filing Date:	05 February 1997 (05.02.97)	:
For:	COMPOSITION AND METHOD FOR EFFECTING SUPERFICIAL CHEMICAL SKIN PEELS	: Attorney Docket No. **6149-29 PC**

DECLARATION OF DOUGLAS E. KLIGMAN, M.D., Ph.D.

I, Douglas E. Kligman, declare and state as follow:

1. I am the same Douglas E. Kligman who is a named Applicant and joint inventor in the above-identified patent application.

2. I received a Medical Doctor degree from the University of Miami School of Medicine and a Doctor of Philosophy in Cell Biology from the University of Washington School of Medicine. My medical practice specialty is Dermatology, in which I am Board Certified. A significant area of my research and dermatology practice involves superficial chemical skin peeling for treatment of skin disorders. A copy of my *Curriculum Vitae* is attached hereto.

3. Based upon my education, professional experience, research and clinical practice, I believe that I am considered to be an expert in the use of superficial chemical skin peeling techniques for the treatment of skin disorders.

4. I am familiar with the Written Opinion dated October 17, 1997 for the above-noted International Patent Application No. PCT/US97/01919 and with the Authorized Officer's statement that claims 15-19 lack novelty over Henderson, U.S. Patent 5,296,476 and that claims 1-14 lack inventiveness over Henderson '476 and Brody, "Chemical Peeling," Mosby Yearbook, Inc., St. Louis, MO, pp. 53-73 (1992).

5. The skin care composition in Henderson '476 that appears to be most pertinent to our claimed invention is a hard corn remover whose formulation is shown at column 4, lines 21-25 of Henderson '476. This formulation is the only one containing more than 10 wt% salicylic acid. I have found no support for the Authorized Officer's assertion that Henderson '476 teaches the use of 2-50 % salicylic acid, at column 3, lines 60-61 or elsewhere. The hard corn remover formulation of Henderson '476 has the following composition:

micronized calcium citrate	10-40 wt%
salicylic acid	10-20 wt%
ethyl alcohol	30 wt%
bentonite	5 wt%
water	sufficient to make 100 wt %

6. In order to respond to the Authorized Officer's comments about the pertinence of this reference, I first prepared four formulations whose compositions satisfied the requirements for the hard corn remover formulation as described by Henderson '476 (noted above). The Henderson '476 hard corn remover describes ranges for two of its components, namely, micronized calcium citrate and salicylic acid, so the four formulations I prepared contained representative values of these two components: 40 wt% and 10 wt% calcium citrate and 20 wt% and 15 wt% salicylic acid. The two values selected for calcium citrate represent the upper and lower limits of this component in the Henderson '476 hard corn remover formulation, and the two values selected for salicylic acid represent the maximum amount and midrange amount of this component in the Henderson '476 hard corn remover formulation. A value of 15 wt% salicylic acid also represents the lower limit of salicylic acid specified for the present invention.

The compositions of the four Henderson '476 hard corn remover formulations ("Henderson formulations") that I prepared were as follows:

Henderson No. 1

micronized calcium citrate	10 wt%
salicylic acid	15 wt%
ethyl alcohol	30 wt%
bentonite	5 wt%
water	40 wt %

Henderson No. 2

micronized calcium citrate	10 wt%
salicylic acid	20 wt%
ethyl alcohol	30 wt%
bentonite	5 wt%
water	35 wt %

Henderson No. 3

micronized calcium citrate	40 wt%
salicylic acid	15 wt%
ethyl alcohol	30 wt%
bentonite	5 wt%
water	10 wt %

Henderson No. 4

micronized calcium citrate	40 wt%
salicylic acid	20 wt%
ethyl alcohol	30 wt%
bentonite	5 wt%
water	5 wt%

7. These four formulations of the Henderson '476 hard corn remover were prepared by mixing appropriate amounts of calcium citrate (very fine powdered calcium citrate tetrahydrate, 97.5-100.5% dry basis, obtained from Spectrum Quality Products, New Brunswick, NJ), salicylic acid (99% ACS reagent grade crystalline powder, obtained from Aldrich Chemical Company, Milwaukee, WI), 30 ml ethanol (absolute ethanol, 95%), bentonite (a fine clay powder obtained from Aldrich Chemical Company, Milwaukee, WI) and water. The three powdered solid components were combined with vigorous agitation with the ethanol and water components at ambient temperature. The resulting

Henderson formulations were observed to be viscous slurries, *i.e.*, thick suspensions of tannish brown solids in the liquid.

8. Three formulations ("Kligman formulations") representative of the compositions used in the method of this invention were also prepared, to provide a basis for comparison in this study. The three Kligman formulations contained 15 wt% salicylic acid, 20 wt% salicylic acid, and 25 wt% salicylic acid dissolved in ethanol (absolute ethanol, 95 %) as the solvent. The Kligman formulations used only ethanol as the solvent, and no water was added to these three formulations. The Kligman formulations were clear solutions, in contrast to the Henderson formulations which were viscous suspensions.

9. The Henderson '476 formulations and Kligman formulations were next used to treat six individuals whose facial skin exhibited moderate photodamage. Each subject was treated with two formulations, one Henderson formulation and one Kligman formulation, one on each cheek. The treatment protocol taught at pages 16-17 of the above-identified patent application was followed: each of the formulations was applied with cotton tipped applicators to the mid cheek and left on the cheek for three minutes, after which time the treated sites were washed with water.

10. When the Henderson formulations were applied to the facial skin of the six subjects, subjects being treated experienced very minimal stinging or burning sensation. The level of stinging and/or burning was far less than that experienced with the three Kligman formulations of the present invention.

11. Follow-up examination of the treated subjects was conducted at 48-72 hours after treatment, to determine whether peeling had occurred as a result of the treatment. This examination revealed, for the skin sites treated with any of the four Henderson formulations, that there were no adverse events of the treated skin such as erythema, pain and/or swelling. More importantly, however, it was noted that there was no change in the texture or quality of the skin sites treated with any Henderson formulation, and no peeling (desquamation) was observed to have occurred at these sites. Desquamation

signals that shedding of a surface skin layer has occurred and is regarded as a clinical endpoint that demonstrates the effectiveness of a skin treatment with a putative chemical skin peeling agent. In the absence of desquamation, a skin treatment material cannot be regarded as a useful chemical skin peeling agent under the conditions being evaluated.

12. The absence of any skin peeling or skin improvement with the four Henderson formulation contrasted with the different results obtained with the three Kligman formulations evaluated in this study. Subjects whose facial skin was treated with the three Kligman formulations, 25 wt%, 20 wt% and 15 wt% salicylic acid solutions in ethanol, were observed at the 48-72 hour examination to exhibit slight desquamation, indicating that peeling of the treated skin had begun. These results are consistent with the results described at pages 16-17 in the Example of the present application, in which a concentrated salicylic acid solution was used according to this invention.

13. These experimental results, in which the Henderson hard corn remover formulations proved to be ineffective as an agent for superficial chemical skin peeling, were surprising to me in that the Henderson formulations failed to demonstrate skin peeling activity, notwithstanding the fact that these prior art formulations contained the same salicylic acid concentrations as did the Kligman salicylic acid solutions that were also evaluated at the same time. These results, in my opinion, confirm the unexpected and surprising results associated with the composition and method of the claimed invention and demonstrate that the concentrated salicylic acid solution and skin peeling method of this invention represent a remarkable and surprising advance in the art of chemical skin peeling.

14. With respect to the teachings of the cited Brody reference, these teachings are generally similar to the results of the Swinehart study, in which salicylic acid was used for treatment of photodamaged skin on the hands and forearms, in the form of a salicylic acid paste or ointment. Such treatments involve application of a thick coating of ointment, containing 50% salicylic acid, to the affected skin, then wrapping the treated areas with Saran Wrap® plastic wrap secured with tape, followed by a 48 hours occlusion period after which the dressing is removed; see Swinehart, "Salicylic Ointment Peeling of the Hands

and Forearms", *J. Dermatol. Surg. Oncol. 18*, pp. 495-498 (1992). The inconvenience of this treatment for photodamaged skin on hands and forearms is self-evident and is unacceptable for many patients.

15. A treatment such as described by Swinehart (mentioned in Brody) is clearly inappropriate for treatment of facial skin, and I am unaware of any reports of such a treatment ever having been carried out on a person's face. This is not surprising since facial skin is much thinner that skin on a person's arms, and this procedure is subject to a risk of salicylism, *i.e.*, toxic effects from systemic absorption of salicylic acid during the prolonged treatment period. The use of a salicylic acid paste or ointment as described by Swinehart, also mentioned by Brody, for treating damaged skin on the hands and forearms is, in my opinion, a procedure that has very limited applicability because of its drawbacks as just described. This treatment using a salicylic acid ointment or paste is completely unrelated to the concentrated salicylic acid solutions of the present invention and their use in skin peel treatments of short duration.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

12/16/97
(Date)

Douglas E. Kligman, M.D., Ph.D.

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Board Certified, Dermatology	1994
National Board Medical Examiners Certification	1991

EDUCATION AND TRAINING:

Dermatology Residency Thomas Jefferson University Hospital Philadelphia, PA	1991-1994
Transitional Residency, Lancaster General Hospital Lancaster, PA	1990-1991
M.D., University of Miami School of Medicine	1990
Ph.D., Cell Biology, University of Washington School of Medicine	1980
B.A., Biological Sciences, University of California (Berkeley)	1974

MEDICAL LICENSURE:

Pennsylvania Licensure	1994
National Board of Medical Examiners, Certificate	1991

PROFESSIONAL EXPERIENCE:

Clinical Investigator, S.K.I.N, Inc.	1994 - Present
Dermatologist, Chestnut Hill Hospital, Phila. Pa	1994 - Present
Senior Staff Fellow, National Institutes of Health	1984-1988
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MEMBERSHIP IN PROFESSIONAL ORGANIZATIONS:

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